AHPA
AMERICAN HERBAL PRODUCTS ASSOCIATION

February 17, 2009

Barbara Shane, Ph. D.
NTP Executive Secretary
NIEHS/NIH
PO Box 12233 - MD K2-03
Research Triangle Park, NC 27709
via email: *shane@niehs.nih.gov*

Re: Written Comments on TR 562

Dear Dr. Shane,

This correspondence serves as written comments on NTP Technical Report on the Toxicology and Carcinogenesis Studies of Goldenseal Root Powder (*Hydrastis canadensis*) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 562, scheduled for peer review on February 25, 2009. These comments are submitted on behalf of the American Herbal Products Association (AHPA).

I am aware that written comments on TR 562 were requested to be submitted by February 11, 2009, and I appreciate your willingness to accept this communication after that date.

The comments submitted here are limited to the specific issue of the levels of exposures to goldenseal root powder by humans identified in TR 562. TR 562 on page 89 states that "exposure concentrations used in the 2-year studies overlapped estimated human exposures." This assertion is based on a human exposure described in TR 562 as 1,000 mg of goldenseal three times a day in a 70 kg man. The reference for this level of human exposure is given in TR 562 as "NSD, 2007."

The reference identified as "NSD, 2007" is listed in TR 562's references, on page 105, as "Natural Standard Databases (NSD) (2007). Foods, Herbs, and Supplements Database: Berberine. Natural Standard Monograph, National Standard, Inc., <http://www.naturalstandard.com>. Website accessed December, 2007." This monograph is on the alkaloid berberine, however, and does not, in fact, provide any dosage information for goldenseal root, but only for berberine and berberine compounds. This monograph states, without references, that berberine may be or has been taken orally at levels up to 2 grams daily for 8 weeks, and at a dose of 0.5 gram twice daily for 3 months; that berberine sulfate

has been used at a single dose of 400 milligrams; and that berberine bisulfate has been used at a dose of 5 milligrams three times daily for 15 days. Doses are also provided for injection of berberine and for use of berberine in eye drops.

Although berberine is a constituent in goldenseal root, information on the dosage of berberine is not directly correlated to doses of goldenseal root, and the cited reference makes no attempt to draw any such correlation. It is of course possible that the authors erred in their identification of the cited reference, and recognizing this possibility, the Natural Standard Databases monograph on goldenseal was reviewed in preparation for submission of these comments.

This separate monograph (the title is: "Goldenseal (Hydrastis Canadensis L.), Berberine," Natural Standard Monograph, © 2008) provides information, again without references, for adult dosage in tablet or capsule form as: "0.5-1 gram of goldenseal three times daily has been used historically, although safety and efficacy have not been demonstrated in clinical trials." This document also identifies a referenced study in which human subjects consumed 4 capsules of a product reported to contain 535 milligrams of goldenseal root (2.14 grams) for a single day.

But if this Natural Standard Monograph on goldenseal is the one that was intended to be cited in TR 562, its unreferenced identification of goldenseal root's "historical" daily adult dosage is inconsistent with more authoritative references. For example, the American Herbal Pharmacopoeia (AHP) published a monograph on goldenseal root in 2001. (In the interest of full disclosure, I am an AHP board member.) The AHP monograph identifies the daily dose of goldenseal root as 2 grams, and cites the 1946 edition of the *National Formulary* (NF). This monograph also provides doses, again referenced to the 1946 NF, for goldenseal root in the form of a tincture and a fluid extract at levels equivalent to 1.6 to 2 grams per day of the root.

Another factor to consider in determining the relevance of human exposures to goldenseal root is the duration of use. Goldenseal is not generally used on a daily and long-term basis, and it is highly unlikely that it would be consumed every day during a two year period, or for any substantial portion of the 730 days in a two year period.

In summary, the level of human exposure to goldenseal root identified in TR 562 is 50 percent higher than the level recorded in contemporary and historical authoritative references, and TR 562 has not taken into account the fact that humans do not use goldenseal root on a continuing long-term basis. The conclusion that "exposure concentrations used in the 2-year studies overlapped estimated human exposures" should be reconsidered.

Thank you in advance for considering the information provided in these comments.

Sincerely,

Michael McGuffin
President, American Herbal Products Association
8630 Fenton Street, Suite 918
Silver Spring, MD 20910
(301) 588-1171 x201